Tetrahedron 67 (2011) 9265–9272

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A biomimetic synthesis of (−)-ascorbyl phloroglucinol and studies toward the construction of ascorbyl-modified catechin natural products and analogues

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ARTICLE INFO

Article history:
Received 3 August 2011
Received in revised form 20 September 2011
Accepted 21 September 2011
Available online 28 September 2011

Keywords:
(−)-Ascorbyl phloroglucinol
Ascorbyl epigallocatechin
Ascorbylation reaction
Stereoselective reaction
Chemoselective reaction

ABSTRACT

A method for appending the ascorbyl moiety onto the framework of phenolic natural products has been developed. This reaction proceeds in two steps from L-ascorbic acid and employs acetic acid catalysis. Excellent stereoselectivity is observed during C–C bond formation between the phenolic compound and dehydroascorbic acid, and the process is also chemoselective for phenol derivatives bearing electron-donating substituents in each of the 1, 3, and 5 positions. Further, good regioselectivity was also observed when phenols lacking an axis of C_2 symmetry were employed. This method has led to the synthesis of (−)-ascorbyl phloroglucinol as well as the tetracyclic core of ascorbyl-modified catechin natural products.

1. Introduction

Polyphenols produced by tea plants are well known to have a range of interesting and medicinally relevant bioactivities. Members of this class of molecules have been reported to be potent antiobesigens,[1] antivirals,[2] antioxidants,[3–5] and anticarcinogens,[6] and also display other desirable properties.[6–9] Many of these activities have been ascribed to catechin-derived molecules, and a series of ascorbyl-modified catechins have been reported. These natural products display a range of complexity from the simple ascorbylated phloroglucinol, (−)-ascorbyl phloroglucinol (**1a**), to more complex ascorbylated catechins (Fig. 1).[10] While the full spectrum of biological activities displayed by molecules of this class have not been fully explored, 8-*C*-ascorbyl-(−)-epigallocatechin **2a** has been shown to be effective in stopping the replication of HIV in vivo with an EC_{50} of 8.33 μM and for inhibiting pancreatic lipases in vitro with an IC_{50} of 0.646 μM.

(−)-Ascorbyl phloroglucinol **1a** has previously only been isolated as the corresponding peracetate derivative **3**. Prior work has also not been able to unambiguously assign the stereochemical configuration at the tertiary and hemiacetal carbons (C2′ and C3′) for any ascorbylated phenols, although modeling has suggested that the *SSRS* configuration for C2′–5′, respectively, is the most stable for **3**.[11] These intriguing biological data coupled with the interesting structures and open questions concerning the stability and stereochemistry of these molecules led us to pursue the development of a synthetic strategy to construct the tricyclic core of this set of related compounds.

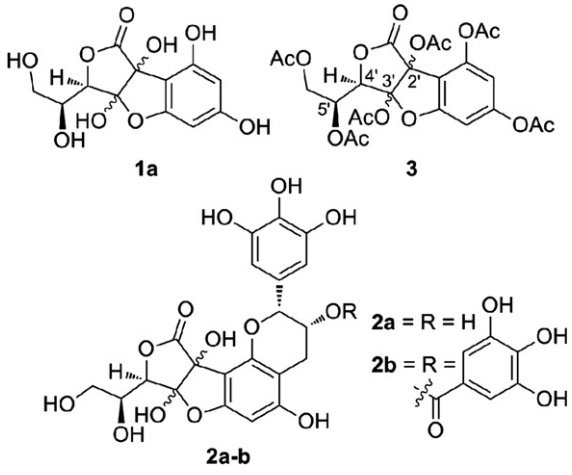

Fig. 1. Natural product structures.

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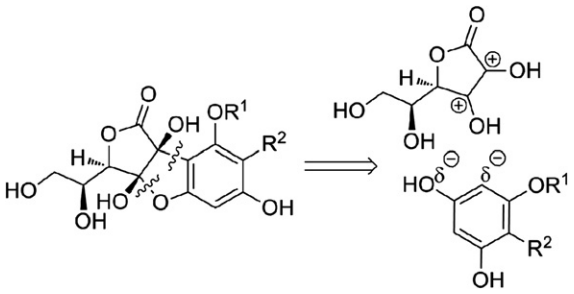
doi:10.1016/j.tet.2011.09.102

2. Results and discussion

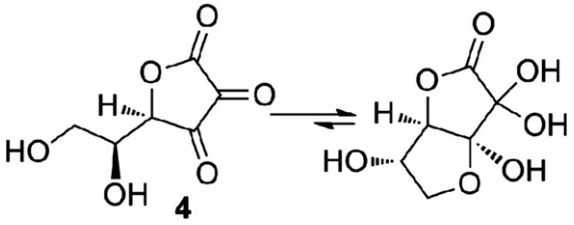
2.1. Retrosynthetic analysis and design rationale

We reasoned that a late-stage introduction of the ascorbyl moiety onto the trioxyarene would be desirable for the construction of these natural products and analogous structures. After observing the structural similarity for the ascorbylated natural products, it became obvious that all of these compounds could be constructed by a similar route in which the C–C bond between the ascorbyl group and the arene were formed if a suitable electrophilic version of ascorbic acid was used (Scheme 1). The natural nucleophilicity of the arene would then provide the other reacting partner. The biosynthesis of these molecules has been proposed to proceed via a similar strategy.[12]



Scheme 1. Retrosynthetic analysis.

Dehydroascorbic acid **4** can be easily generated by the oxidation of ascorbic acid, and this molecule has the desired electrophilic character.[13] This is evidenced by the fact that the carbonyl groups at both C2 and C3 are almost exclusively found to be the hemiacetal or hydrate, respectively (Scheme 2). The observation that the bicyclic hemiacetal predominates also led to the hypothesis that the C–C bond would be formed preferentially from the opposite side of the dihydroxyethyl group of **4** yielding products with the relative stereochemistry shown in Scheme 1. Similar stereoselection has been observed in the reduction of L-ascorbic acid to the corresponding L-gulonic acid γ-lactone.[14]

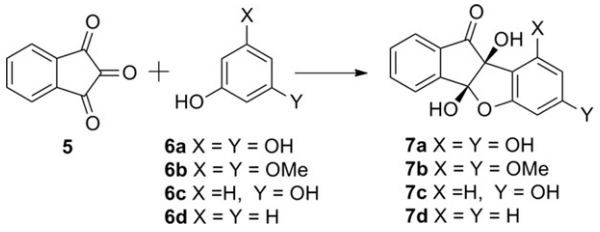


Scheme 2. Reactivity of **4**.

2.2. Reaction of hydroxyarenes with indane 1,2,3-trione

The base-catalyzed addition of phloroglucinol **6a** to **4** has been reported, although the stereochemistry of the product remained ambiguous.[12] In our hands, we were unable to obtain good results for the reaction of **6a** with **4** under basic conditions using $NaHCO_3$, NEt_3, or K_2CO_3. Due to this, we chose to investigate the use of acid catalysis for the addition of hydroxyarenes to **4**. The first step in this process was to determine the relative reactivity of mono-, 1,3-di-, and 1,3,5-trihydroxyarenes [phenol (**6d**), resorcinol (**6c**), and phloroglucinol (**6a**)] with a model 1,2,3-triketone (indane 1,2,3-trione **5**). These reactions have been reported using acetic acid (AcOH) as a catalyst, although a consistent set of conditions had not been evaluated for each molecule.[15,16] To this end, we explored the reactivity of several hydroxyarenes with **5** using AcOH as both the solvent and the catalyst at 60 °C (Table 1). As expected, the reaction rate rose with increasing electron density of the arene. Nucleophiles containing methyl ethers were also able to be successfully used in this reaction. Further, a high yield of product was obtained even when a 1:1 ratio of electrophile and nucleophile was used.

Table 1
Reaction of **5** with hydroxyarenes[a]



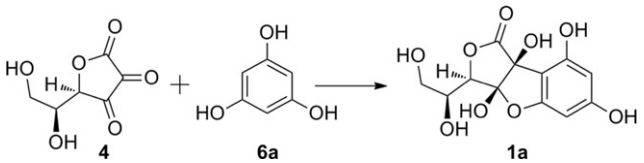
Entry	Arene	Conditions	Temp (°C)	*t* (h)	Yield (%)
1	**6a**	AcOH (neat)	60	2	85
2	**6b**	AcOH (neat)	60	1.5	86
3	**6c**	AcOH (neat)	60	2	80
4	**6d**	AcOH (neat)	60	3	68

[a] The product structures denote relative, not absolute, stereochemistry.

2.3. Optimization of conditions for the addition of 6a to 4

Once the reactivity of the arenes toward addition to **5** had been determined, attention was placed on finding the optimal acid catalyst for the reaction of 1 equiv phloroglucinol with 1 equiv of dehydroascorbic acid, **4**, to give (−)-ascorbyl phloroglucinol **1a**. Initial attempts to perform this transformation in neat AcOH at elevated temperature led to less than desirable yields, and decomposition products were observed. Therefore, this reaction was then attempted using 0.1 equiv of a Lewis acid, either $AlCl_3$ or $BF_3{\cdot}OEt_2$, as the catalyst in THF. No conversion was observed under these reaction conditions, even at elevated temperature (Table 2 entries 1 and 2). Fortunately, **1a** could be obtained in moderate yield when AcOH was used as a co-solvent in THF at either 65 °C for 6 h or at room temperature (rt) for 12 h, although decomposition was still observed at elevated temperature (Table 2 entries 3 and 4). Following from these results, we then found that using a 0.5 equiv excess of dehydroascorbic acid lowered the yield; however, use of a 0.5 equiv excess of arene gave the desired product in 69% yield based on **4** (Table 2 entries 5 and 6). Further, the arene was recoverable in these reactions.

Table 2
Reaction of dehydroascorbic acid with hydroxyarenes



Entry	Arene (equiv)	**4** (equiv)	Conditions	Temp (°C)	*t* (h)	Yield (%)
1	1	1	$AlCl_3$ (0.1 equiv), THF	Reflux	6	NR
2	1	1	$BF_3{\cdot}OEt_2$ (0.1 equiv), THF	Reflux	6	NR
3	1	1	AcOH/THF (2:5 v/v)	Reflux	6	42[a]
4	1	1	AcOH/THF (2:5 v/v)	rt	12	40
5	1	1.5	AcOH/THF (2:5 v/v)	rt	12	26[b]
6	1.5	1	AcOH/THF (2:5 v/v)	rt	12	69[b]

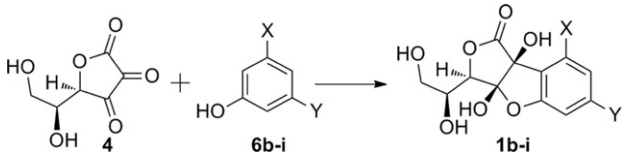
[a] Decomposition was observed.
[b] Yield based on **4**. The arene was recoverable in all cases.

2.4. Probing the arene substrate scope

With optimized conditions for the synthesis of naturally occurring **1a** in hand, we set out to probe the range of hydroxyarenes that could be employed to synthesize other ascorbylated natural products and analogues. On one hand, a high reactivity of dehydroascorbic acid with hydroxyarenes is desirable for the construction of analogues; however, a lack of reactivity toward the pyrogallyl (1,2,3-trihydroxybenzyl) and gallyl (3,4,5-trihydroxybenzoyl) moieties is desirable for the chemoselective synthesis of natural products, such as **2a**,**b**, if strategies employing protecting groups are to be avoided.

To begin this investigation, a series of phenol, resorcinol, and phloroglucinol and their derivatives were reacted with dehydroascorbic acid **4** under the optimized conditions with AcOH as the catalyst (Table 3). Although arenes with a range of electron donating and withdrawing groups were studied, it was found that three electron donating groups were necessary for reaction to proceed with this substrate series (Table 3 entry 1). This is in contrast to the reactions with **5** where even phenol was capable of acting as a suitable nucleophile (Table 1). It was also noted that arenes containing benzyl ethers decomposed under the reaction conditions, and this has implications for further syntheses as discussed below in Section 2.7.

Table 3
Reaction of **4** with hydroxyarenes



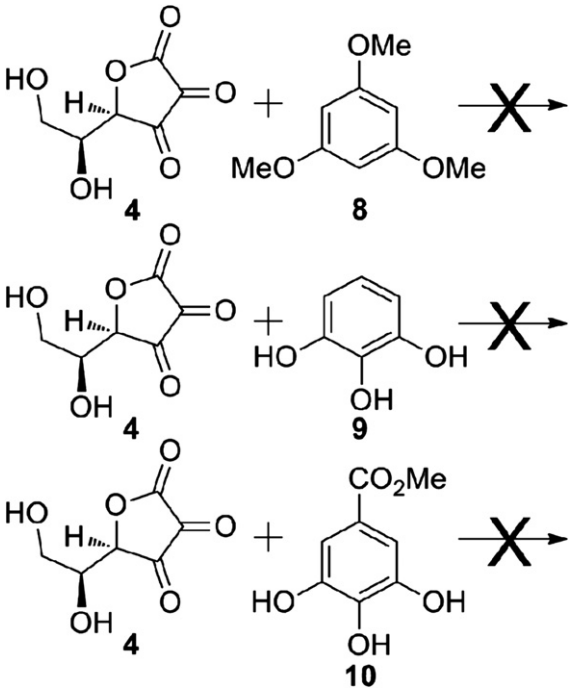
Entry	Arene	X	Y	Yield (%)
1	**6b**	OMe	OMe	72[a]
2	**6c**	H	OH	NR
3	**6d**	H	H	NR
4	**6e**	H	OBn	NR
5	**6f**	H	OAc	NR
6	**6g**	H	OMe	NR
7	**6h**	OBn	OBn	0[b]
8	**6i**	OH	OAc	NR

[a] Yield based on **4**. The arene was recoverable.
[b] The benzylated arene decomposed.

Once it was determined that the arene substrate scope was limited for the series of phenol, resorcinol, and phloroglucinol derived molecules, the reactivities of 1,3,5-trimethoxybenzene (**8**), pyrogallol (**9**), and methyl gallate (**10**) with **4** were explored. None of these arenes displayed any reactivity toward AcOH catalyzed addition to dehydroascorbic acid **4** (Scheme 3). The data obtained from the reactions using **9** and **10** further indicate that the electronic properties of the arene are critical for successful reaction. It is likely that three electron donating groups which all direct addition to the same position on the arene ring are needed and that the presence of any electron withdrawing group hinders reaction. These conclusions are further supported by the data obtained using the bicyclic analogues discussed in Section 2.7. The lack of reactivity between **4** and **8** is also suggestive that hemiacetal formation is necessary to bring the reactants into close proximity before C–C bond formation can occur.

2.5. Structural characterization of (−)-ascorbyl phloroglucinol 1a

Previous attempts to isolate **1a** from natural sources employed peracetylation, presumably to aid in purification.[11] In our hands, **1a**



Scheme 3. Chemoselectivity for reaction with **4**.

was found to be amenable to standard purification techniques, including flash chromatography on silica, as long as alcohols were not used as the solvent in the presence of an acid source. If MeOH was used to elute the column, the presence of an extra methoxy group could be observed in the ^{1}H NMR spectrum, presumably arising from the formation of an acetal at C3′ (data not shown). To confirm that the material obtained from the reaction of **4** with phloroglucinol was the structurally identical to naturally occurring (−)-ascorbyl phloroglucinol, product **1a** was peracetylated and both the ^{1}H and ^{13}C NMR spectra were compared to those reported for the derivatized natural product, and it was found that all resonances matched the reported values.[11]

The reactions leading to both (−)-ascorbyl phloroglucinol **1a** and the methylated analogue **1b** proceeded to yield a single product, although the exact stereochemical configurations at C2′ and 3′ were still ambiguous. The stereochemistry for carbons 2′, 3′, 4′, and 5′ had previously been hypothesized to be *SSRS* based on NOE data and structural modeling of **3** using the SYBYL software package.[11] To obtain more robust evidence for the stereochemistry, the crystallization of both **1a** and **1b** was attempted. These efforts were unsuccessful for **1a**; however, upon standing in hexanes/ethyl acetate colorless needle-shaped crystals of **1b** were obtained. The configuration of **1b** was determined to be *SRRS* from crystallographic data (Fig. 2). Based on these data and precedent from the reduction of ascorbic acid to gulonic acid-γ-lactone, we hypothesize that the addition of the arene to the side of **4** opposite the dihydroxyethyl side chain will be a general feature of these reactions.

2.6. Synthesis of the ascorbylcatechin tetracyclic core

Once the substrate scope and stereochemical outcome had been determined for the reactions leading to tricyclic products, such as phloroglucinol **1a**, reactions using bicyclic arenes were investigated to determine the constraints on the construction of the tetracyclic core of the ascorbylated catechins. A set of four hydroxylated chroman and chroman-4-ones was used, and only one of these

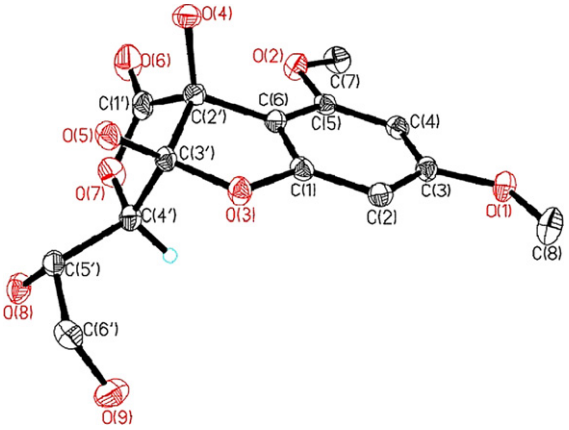
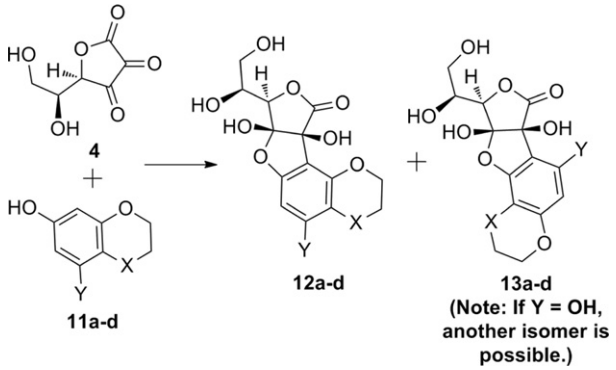


Fig. 2. ORTEP for **1b**.

molecules, chroman-5,7-diol (**11c**), was able to successfully react with **4** (Table 4). These bicyclic substrates fit the constraints observed for reactions with the substituted arenes discussed previously in that three activating groups that all direct to the same position are needed for reaction and no deactivating groups can be tolerated.

Table 4
Reaction of **4** with bicyclic hydroxyarenes



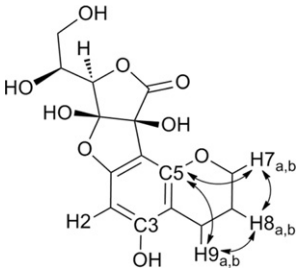
Entry	Arene	X	Y	Product Ratio	Yield (%)
1	**11a**	CH_2	H	NA	NR
2	**11b**	C=O	H	NA	NR
3	**11c**	CH_2	OH	1.88:1 (**12c**/**13c**)	72
4	**11d**	C=O	OH	NA	NR

Regioisomers can be generated upon reaction of **4** with **11c**. One of these isomers, **12c**, corresponds to the desired tetracylic core of the natural products **2a**,**b**, while the other ring system, as in **13c**, has not been shown to be a naturally occurring compound. (Note, if Y is a hydroxyl, e.g., as in **13c** and **13c′** in Table 6, two possible hemiacetals could be generated and may interconvert after rotation around the C–C bond formed during the reaction of the arene with **4**.) In our hands, an ~2:1 mixture of two molecules was obtained when **11c** was reacted with **4** using the conditions optimized for the reaction of **1a**. These molecules were separable by flash chromatography on silica gel, and a battery of 1D and 2D NMR experiments allowed the structure of both to be elucidated (see Supplementary data).

2.7. Structural characterization of 12c and 13c

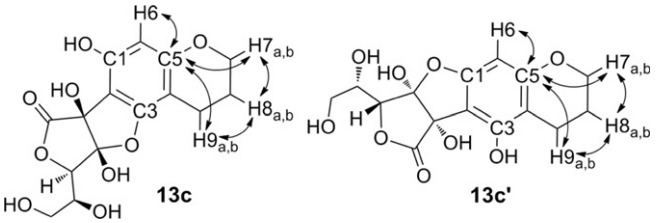
Of the experiments, $^{1}H-^{1}H$ correlation spectroscopy (COSY) and $^{1}H-^{13}C$ heteronuclear multiple-bond correlation spectroscopy

Table 5
Selected COSY and HMBC data for **12c**



Atom	δ_H, mult, J=Hz	δ_C	COSY	HMBC
H7	4.20, m	—	H8	C8, C9, C5
H8	1.98, m	—	H7, H9	C7, C9, C4
H9	2.54, m	—	H8	C7, C8, C3, C4, C5
H2	6.13, s	—	—	C1, C3, C4, C6
H6	—	—	—	—
C5	—	153.7	—	H7, H9

Table 6
Selected COSY and HMBC data for **13c** or **13c′**



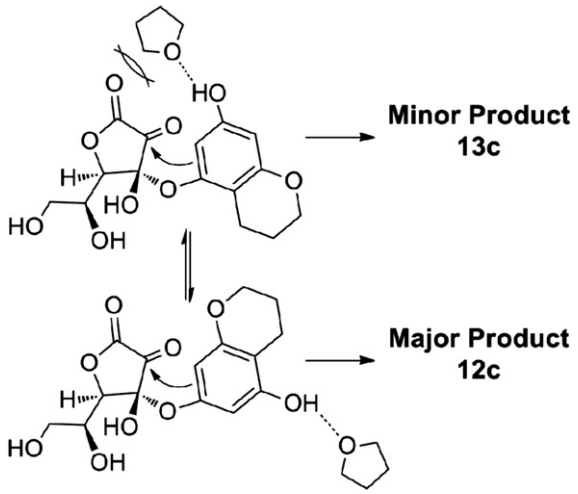
Atom	δ_H, mult, J=Hz	δ_C	COSY	HMBC
H7	4.17, t, J=5.2	—	H8	C8, C9, C5
H8	1.94, m	—	H7, H9	C7, C9, C4
H9	2.54, t, J=6.3	—	H8	C7, C8, C3, C4, C5
H2	—	—	—	—
H6	6.03, s	—	—	C1, C2, C4, C5
C5	—	158.2	—	H7, H9, H6

(HMBC) were the most useful, and it was concluded that **12c** and **13c** were the major and minor component, respectively (Tables 5 and 6 and associated Figs.). The ^{1}H peak shifts and correlations in the COSY experiment allowed H7, H8, and H9 to be identified for each molecule. With these data in hand, the peak for C5 could be assigned from the HMBC experiment based on chemical shift and coupling with H7 and H9. The connectivity of **12c** and **13c** (or **13c′**) could then be determined from the HMBC data, and the molecules could be readily differentiated. For the skeleton of **12c**, only a pair of two or three bond $^{1}H-^{13}C$ couplings involving C5 are possible between this atom and both H7 or H9. In contrast, a trio of two or three $^{1}H-^{13}C$ couplings should be observed for C5 of either **13c** or the isomer **13c′** since the aromatic proton H6 is also able to couple with this key carbon atom along with both H7 and H9. Indeed, the HMBC data were consistent with the expected proton-C5 coupling patterns for both **12c** and **13c**, although **13c** and **13c′** could not be distinguished via NMR spectroscopy.

Both molecular mechanics (MMX[17]) and density functional theory (DFT) calculations were performed to determine the relative conformational stabilities of **12c**, **13c**, and **13c′**. Solvation was not considered in either case. PCModel v. 4.0 (Serena Software) was used for the MMX calculations, and intramolecular hydrogen bonding was maximized among all hydroxyl groups. MMX predicted **13c** to be 1.1 kcal/mol more stable than either **12c** or **13c′**,

which were within 0.2 kcal/mol of each other. The DFT calculations were performed at the B3LYP/6-31+G* level of theory[18] with Gaussian 03,[19] and the structures determined by MMX were used as starting geometries. Again, **13c** was found to be more favorable than **13c′** by 1.0 kcal/mol, and both were found to be lower in energy than **12c** by 7.5 and 6.5 kcal/mol for **13c** and **13c′**, respectively. These results suggest that the reaction may be under kinetic control and that **13c** is the most likely structure for the minor isomer, although this has not been confirmed.

However, it should be noted that the energies calculated for all molecules by MMX could be altered by up to 8 kcal/mol by breaking hydrogen bonding with negligible geometry changes. This highlights the fact that core of these structures are similar in energy. Further, intramolecular hydrogen bonding networks are typically disrupted in hydrogen bonding solvents, such as the 5:2 AcOH/THF (v/v) solution used for this reaction, and it is possible that solvation of either the C1 or C3 hydroxyl in the intermediate(s) increases steric interactions during the formation of either **12c** or **13c**, as exemplified for C1 in Scheme 4. Such solvation effects, which were ignored during the calculations described above, could explain the formation of the product with the lowest gas phase stability under the reaction conditions employed in this study.



Scheme 4. Solvation effect during the reaction of **4** with **11c**.

While the reaction of **11c** with **4** yielded **12c** with the naturally occurring tetracyclic core as the major product, the fact that this molecule was only 65% of the isolated material led us to investigate whether protection at the hydroxyl on the carbon that would become C3 would shift the selectivity further toward **12c** due to sterics. Unfortunately, the construction of either C3 benzylated or silylated hydroxylated chromans proved difficult due to lability of the protecting group (data not shown). These observations are consistent with the decomposition of dibenzylated arene **6b** under the reaction conditions, and they highlight the good leaving group ability of trioxyarenes.

3. Conclusion

A method utilizing readily available **4** for the biomimetic ascorbylation of phenolic natural products has been reported herein. This reaction was found to be stereo-, chemo-, and regioselective, and a synthesis of the natural product, (−)-ascorbyl phloroglucinol (**1a**), was accomplished. Data obtained from the crystal structure of **1b** corroborate previous theoretical assignment of the configuration for the stereocenters at the ascorbyl–phenol junction in compounds of this type. Further, the tetracyclic core of ascorbylated catechins, such as 8-*C*-ascorbyl-(−)-epigallocatechin, was constructed. Efforts are underway to evaluate the bioactivity of the molecules reported herein and to expand the scope of this methodology to the construction of more complex ascorbylated natural products and analogues.

4. Experimental

4.1. Materials and general methods

All reagents and solvents were purchased from Fisher Scientific and used without further purification unless noted. Silica gel (60 Å, 40–63 μm, 230×400 mesh) and polyester backed thin-layer chromatography (TLC) plates (Silica G w/UV, 200 μM) were purchased from Sorbent Technologies. All reactions were carried out under nitrogen unless otherwise stated. All 1D ^{1}H and ^{13}C spectra were recorded using a 300 MHz Varian Mercury or 500 MHz Varian INOVA spectrometer. Deuterated solvents used for NMR analyses were purchased from Cambridge Isotope Laboratories. The NMR chemical shifts are reported in parts per million (ppm) and referenced to the solvent peak. All 2D NMR spectra were recorded on a 600 MHz Varian INOVA. IR spectra were obtained on a Varian 4000 FT-IR instrument. High-resolution mass spectra (HRMS) were obtained with an Applied Biosystems MDS Sciex Qstar Elite time-of-flight mass spectrometer (MS), and optical rotations were recorded using a Perkin–Elmer 241 polarimeter. Data for the X-ray crystal structure of **1b** were collected on a Bruker-AXS Smart APEX II diffractometer fitted with a Nicolet LT-2 low temperature device and a graphite-monochromated Mo Kα radiation at 0.71073 Å.

*4.1.1. General procedure for the reaction of hydroxyarenes with **5** (**7a–d**).* These reactions were carried out via slight modifications of previously reported procedures.[15,16] Ninhydrin (1.00 mmol) and the appropriate hydroxyarene (1.00 mmol, **6a–d**) were placed in a round-bottom flask and dissolved in 3 mL of AcOH. If the reagents were not completely soluble, THF was added dropwise until the mixture was homogeneous. The solution was then refluxed for 2–3 h. At this time, the reaction mixture was cooled to rt and diluted with 10 mL H_2O. The product was isolated after extractions of the aqueous layer with ethyl acetate (EtOAc, 3×15 mL). The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The resulting crude product was purified by column chromatography on silica gel using 20% acetone in CH_2Cl_2 as the eluent.

*4.1.1.1. 4b,7,9,9b-Tetrahydroxy-4bH-indeno[1,2-b]benzofuran-10(9bH)-one (**7a**) and 4b,9b-dihydroxy-4bH-indeno[1,2-b]benzofuran-10(9bH)-one (**7d**).* These molecules have been reported previously,[15,16] and all analytical data collected for these studies matched those in the literature.

*4.1.1.2. 4b,7,9b-Trihydroxy-4bH-indeno[1,2-b]benzofuran-10(9bH)-one (**7c**).* R_f (30% acetone/CH_2Cl_2) 0.68; mp=226 °C; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1150, 1466, 1499, 1626, 1731, 2957, 3280–3580 (br); ^{1}H NMR (500 MHz, acetone-d_6, δ): 8.62 (s, 1H), 7.98 (d, J=7.8 Hz, 1H), 7.88 (t, J=7.5 Hz, 1H), 7.74 (d, J=7.7 Hz, 1H), 7.69–7.58 (m, 1H), 7.26 (d, J=8.3 Hz, 1H), 6.55 (s, 1H), 6.44 (dd, J=8.3, 2.2 Hz, 1H), 6.25 (d, J=2.2 Hz, 1H), 5.65 (s, 1H); ^{13}C NMR (126 MHz, acetone-d_6, δ): 161.0, 158.7, 148.9, 136.3, 134.5, 130.7, 126.2, 124.9, 122.8, 116.3, 109.1, 97.3, 82.2; HRMS-ESI (m/z): $[M-H]^-$ calcd for $C_{15}H_{10}O_5$, 269.0450; found, 269.0454.

*4.1.1.3. 4b,9b-Dihydroxy-7,9-dimethoxy-4bH-indeno[1,2-b]benzofuran-10(9bH)-one (**7b**).* R_f (30% acetone/CH_2Cl_2) 0.79; mp=204 °C; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1152, 1466, 1497, 1623, 1734, 2956, 3419; ^{1}H NMR (500 MHz, acetone-d_6, δ): 7.93 (d, J=7.2 Hz, 1H), 7.84 (t, J=7.0 Hz, 1H), 7.73 (d, J=7.3 Hz, 1H), 7.63 (d, J=7.0 Hz, 1H), 6.45 (s, 1H), 6.06 (s, 1H), 6.00 (s, 1H), 5.52 (s, 1H), 3.77

(s, 3H), 3.72 (s, 3H); ^{13}C NMR (126 MHz, acetone-d_6, δ): 196.9, 164.3, 159.8, 159.2, 148.1, 135.9, 131.0, 124.7, 122.8, 110.5, 104.6, 93.9, 92.0, 88.2, 83.3, 55.0, 54.9; HRMS-ESI (m/z): [M−H]$^-$ calcd for $C_{17}H_{13}O_6$, 313.0712; found, 313.072.

*4.1.2. Preparation of L-dehydroascorbic acid (**4**).* This material was prepared via a slight modification of a known procedure.[13] Briefly, iodine (1.40 g, 5.68 mmol) was added in one portion to a stirring solution of L-ascorbic acid (1.00 g, 5.68 mmol) dissolved in methanol (10 mL), and the reaction mixture was allowed to stir for 10 min at rt. At this time, lead carbonate (3.40–3.65 g) was added slowly to the brown reaction mixture until it turned colorless. The resulting mixture was filtered through Celite to remove the bulk of the Pb, and the filtrates were then treated with H_2S to precipitate the remaining metal. The resulting solids were removed from the filtrate by a second filtration through Celite, and air was blown through the crude solution containing **4** to remove excess H_2S. Concentration *in vacuo* gave the desired product as a white, sticky solid in ~25% yield and sufficient purity to be used in further reactions. Partial characterization of this material has been reported previously.[13] ^{1}H NMR (300 MHz, D_2O, δ): 4.55 (ddd, J=5.2, 2.7, 0.8 Hz, 1H), 4.24 (dd, J=10.4, 2.6 Hz, 1H), 4.12 (dd, J=10.4, 2.6 Hz, 1H), 3.70–3.74 (m, 1H).

*4.1.3. Chroman-5,7-diol (**11c**).* Phloroglucinol **6a** (1.00 g, 7.93 mmol) was placed in a round-bottom flask and dissolved in 10 mL of aqueous 2 N NaOH at rt. An ethanolic solution of 1,3-dibromopropane (0.881 mL, 8.72 mmol dissolved in 10 mL) was then added slowly, and the reaction mixture was stirred for 10 h at rt. At this time, the reaction was cooled to 0 °C with an ice bath and then acidified using 1 N HCl to pH 2. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were then dried with $MgSO_4$ and filtered. The resultant supernatants were concentrated under vacuum to give a crude liquid, which was then purified via flash silica chromatography using 20% acetone in CH_2Cl_2 as the eluent. This procedure yielded 0.450 g of **11c** as a pure, amorphous white solid (34%). R_f (30% acetone/CH_2Cl_2) 0.75; mp=176 °C; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 949, 1189, 1278, 1475, 1521, 1621, 2975, 3100–3480 (br); ^{1}H NMR (500 MHz, acetone-d_6, δ): 8.02 (s, 1H, OH), 7.83 (s, 1H, OH), 5.96 (d, J=2.3 Hz, 1H, Ar–H), 5.79 (d, J=2.3 Hz, 1H, Ar–H), 4.07–3.96 (m, 2H, –OCH_2CH$_2$CH$_2$–), 2.52 (t, J=6.6 Hz, 2H, –OCH$_2$CH$_2$CH_2–), 1.94–1.77 (m, 2H, –OCH$_2$CH_2CH$_2$–); ^{13}C NMR (126 MHz, CD_3OD, δ): 156.2, 156.0, 155.9, 101.3, 94.5, 94.4, 94.4, 65.8, 22.0, 18.5; HRMS-ESI (m/z): [M−H]$^-$ calcd for $C_9H_9O_3$, 165.0552; found, 165.0557.

*4.1.4. 5,7-Dihydroxychroman-4-one (**11d**).* This preparation follows a known procedure that employed resorcinol **6c**.[20] Phloroglucinol **6a** (0.88 g, 7.00 mmol) and 3-chloropropionic acid (0.83 g, 7.70 mmol) were dissolved in 2.7 mL of triflic acid. The reaction mixture was then heated at 80–90 °C for 1 h. At this time, the reaction was cooled to rt and diluted with EtOAc (20 mL). The resulting mixture was then poured onto ice (~60–70 g), and a precipitate formed. The entire mixture was extracted with EtOAc (3×20 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to give 3-chloro-1-(2,4,6-trihydroxyphenyl)propan-1-one as an orange oil that was of sufficient purity to be used directly in the next step. This intermediate was then placed in a round-bottom flask and cooled to 0 °C in an ice bath. 2 N NaOH (50 mL) was then added slowly to the reaction vessel, and the resulting mixture was stirred at rt for 2 h. At this time, the reaction was cooled to 0 °C and acidified to pH 2 with 6 N H_2SO_4. The crude product was first purified by extraction with EtOAc (3×25 mL); and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. This material was purified by flash chromatography using silica gel eluted with 20% acetone in CH_2Cl_2 to give 146 mg **11d** as an amorphous, pale-yellow solid (11%). Partial characterization of this material has been reported previously.[21] R_f (30% acetone/CH_2Cl_2) 0.76; ^{1}H NMR (300 MHz, DMSO-d_6, δ): 9.67 (s, 1H), 9.39 (s, 1H), 6.11 (d, J=2.3 Hz, 1H), 5.90 (d, J=2.3 Hz, 1H), 2.73–2.62 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6, δ): 196.7, 166.9, 164.0, 163.5, 102.5, 96.1, 95.2, 66.7, 36.3; HRMS-ESI (m/z): [M−H]$^-$ calcd for $C_9H_7O_4$, 179.0344; found, 179.0349.

*4.1.5. General procedure for the ascorbylation of hydroxyarenes (**1a**–**i**, **12a**–**d**, and **13a**–**d**).* Dehydroascorbic acid **4** (0.250 g, 1.43 mmol) was placed in a round-bottom flask and dissolved in THF (5 mL). The phloroglucinol derivative (2.14 mmol, **6a**–**i**) was then added to the reaction in one portion followed by glacial AcOH (2 mL), and the resulting solution was stirred for 8–10 h. At this time, the reaction mixture was concentrated *in vacuo*, and the resulting material was purified via flash silica chromatography using 70% EtOAc in hexanes as the eluent.

*4.1.5.1. (3R,3aR,8bS)-3-((S)-1,2-Dihydroxyethyl)-3a,6,8,8b-tetrahydroxy-3,3a-dihydrofuro[3,4-b]benzofuran-1(8bH)-one (**1a**).* This material was obtained in 69% yield as a white, amorphous solid. R_f (50% EtOAc/hexanes) 0.56; $[\alpha]_D^{25}$ −46 (c 0.01, H_2O); IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1150, 1472, 1633, 1773, 2962, 3256–3430 (br); ^{1}H NMR (600 MHz, D_2O, δ): 6.08 (d, J=1.1 Hz, 1H, Ar–H), 6.06 (d, J=1.8 Hz, 1H, Ar–H), 4.48 (d, J=6.1 Hz, 1H, –OC*H*CHOHCH$_2$OH), 4.21 (dd, J=10.7, 5.3 Hz, 1H, –OCHC*H*OHCH$_2$OH), 3.85 (dd, J=11.8, 4.0 Hz, 1H, –OCHCHOHCH_2OH), 3.74 (dd, J=11.7, 6.4 Hz, 1H, –OCHCHOHCH_2OH); ^{1}H NMR (600 MHz, DMSO-d_6, δ): 9.55 (s, 1H, OH), 9.46 (s, 1H, OH), 7.77 (s, 1H, OH), 6.03 (s, 1H, OH), 5.88 (s, 1H, Ar–H), 5.72 (s, 1H, Ar–H), 4.96 (s, 1H, OH), 4.70 (s, 1H, OH), 4.12 (d, J=4.7 Hz, 1H, –OC*H*CHOHCH$_2$OH), 3.82 (m, 1H, –OCHC*H*O HCH$_2$OH), 3.52 (m, 1H, –OCHCHOHCH_2OH), 3.39 (m, 1H, –OCHCHOHCH_2OH); ^{13}C NMR (151 MHz, D_2O, δ): 174.4, 161.2, 159.1, 156.1, 110.9, 101.4, 97.3, 90.9, 83.3, 78.7, 69.4, 62.1; HRMS-ESI (m/z): [M−H]$^-$ calcd for $C_{12}H_{11}O_9$, 299.0403; found, 299.0403.

*4.1.5.2. (3R,3aR,8bS)-3-((S)-1,2-Dihydroxyethyl)-3a,8b-dihydroxy-6,8-dimethoxy-3,3a-dihydrofuro[3,4-b]benzofuran-1(8bH)-one (**1b**).* This material was generated in 72% yield as a white, crystalline solid. R_f (70% EtOAc/hexanes) 0.43; $[\alpha]_D^{25}$ −82.6 (c 0.01, H_2O); mp=181 °C; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 800, 1107, 1152, 1596, 1789, 2362, 2459, 2568, 2962, 3168, 3305, 3469; ^{1}H NMR (300 MHz, D_2O, δ): 6.20 (d, J=1.9 Hz, 1H, Ar–H), 6.18 (d, J=1.2 Hz, 1H, Ar–H), 4.46 (d, J=6.4 Hz, 1H, –OC*H*CHOHCH$_2$OH), 4.19 (dd, J=10.1, 5.7 Hz, 1H, –OCHC*H*OHCH$_2$OH), 3.88–3.82 (m, 1H, –OCHCHOHCH_2OH), 3.81 (s, 3H, –OCH_3), 3.78 (s, 3H, –OCH_3), 3.72 (m, 1H, –OCHCHOHCH_2OH); ^{1}H NMR (500 MHz, DMSO-d_6, δ): 8.00 (s, 1H, OH), 6.15 (s, 1H, Ar–H), 6.14 (s, 1H, Ar–H), 5.09 (s, 1H, OH), 4.74 (s, 1H, –OC*H*CHOHCH$_2$OH), 4.17 (s, 1H, –OCHC*H*OHCH$_2$OH), 4.02 (s, 1H, OH), 3.86 (s, 1H, OH), 3.74 (s, 6H, –OCH_3), 3.53 (s, 1H, –OCHCHOHCH_2OH), 3.37 (s, 1H, –OCHCHOHCH_2OH); ^{13}C NMR (151 MHz, D_2O, δ): 174.4, 164.8, 159.0, 158.7, 110.9, 102.3, 93.5, 89.4, 83.4, 78.9, 69.4, 62.0, 55.9, 55.8; HRMS-ESI (m/z): [M−H]$^-$ calcd for $C_{14}H_{16}O_9$, 327.0713; found, 327.0713.

*4.1.5.3. Procedure for X-ray analysis of **1b**.* To obtain crystallographic data (Table 7), a suitable crystal was selected and mounted using glue, and the data were collected at 23 °C. The structures were solved by direct methods, and non-hydrogen atoms were anisotropically refined by treating all hydrogen atoms as idealized contributions. Empirical absorption correction was performed with the SADABS software package from Bruker. In addition, global refinements for the unit cell and data reduction of the structure were performed using Saint version 6.02 (Bruker), and all calculations

were performed using the SHELXTL version 5.1 proprietary software package from Bruker. Crystallographic data for **1b** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 827129. These data can be freely obtained from the CCDC by sending an application by email to deposit@ccdc.cam.ac.uk.

Table 7
X-ray crystallographic data for **1b**

Identification code	**1b**
Empirical formula	$C_{14}H_{16}O_9$
Formula weight	328.27
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	a=6.743(5) Å α=90° b=13.829(10) Å β=90° c=14.625(11) Å γ=90°
Volume	1363.7(17) Å^3
Z	4
Density (calculated)	1.584 mg/m^3
Absorption coefficient	0.135 mm^{-1}
F (000)	676
Crystal size	0.05×0.05×0.4 mm^3
Theta range for data collection	2.03–28.46°
Index ranges	$-8\leq h\leq 8$, $-18\leq k\leq 18$, $-19\leq l\leq 19$
Reflections collected	15,452
Independent reflections	3262 [R(int)=0.0374]
Completeness to theta=28.46°	96.7%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3262/0/214
Goodness-of-fit on F^2	1.019
Final R indices [$I>2\sigma(I)$]	$R1$=0.0351, $wR2$=0.0780
R indices (all data)	$R1$=0.0492, $wR2$=0.0848
Absolute structure parameter	−0.1(9)
Largest diff. peak and hole	0.188 and −0.185 e Å^{-3}

*4.1.5.4. (7aR,8R,10aS)-8-((S)-1,2-Dihydroxyethyl)-5,7a,10a-trihydroxy-3,4,7a,8-tetrahydro-2H-furo[3′,4′:4,5]furo[2,3-h]chromen-10(10aH)-one (**12c**).* This material was the major product from reaction of **4** with **11c** and was generated in 47% yield as a white, amorphous solid. R_f (60% acetone/CH_2Cl_2) 0.76;$[\alpha]_D^{25}$ −14 (*c* 0.01, acetone); IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1155, 1455, 1511, 1638, 1775, 2959, 3000–3620 (br); ^{1}H NMR (500 MHz, D_2O, δ): 6.13 (s, 1H, Ar–H), 4.46 (d, J=5.7 Hz, 1H, –OC*H*CHOHCH$_2$OH), 4.20 (m, 3H, –OC*H*$_2$CH$_2$CH$_2$– and –OCHC*H*OHCH$_2$OH), 3.87 (dd, J=11.9, 4.3 Hz, 1H, –OCHCHOHC*H*$_2$OH), 3.75 (dd, J=11.8, 6.5 Hz, 1H, –OCHCHOHC*H*$_2$OH), 2.61–2.47 (m, 2H, –OCH$_2$CH$_2$C*H*$_2$–), 2.03–1.92 (m, 2H, –OCH$_2$C*H*$_2$CH$_2$–); ^{13}C NMR (126 MHz, D_2O, δ): 174.3, 158.3, 156.1, 153.7, 110.5, 105.3, 101.0, 90.4, 87.3, 82.9, 78.8, 76.0, 72.5, 69.2, 66.8, 61.9, 20.8, 18.4; HRMS-ESI (*m*/*z*): [M−H]$^-$ calcd for $C_9H_9O_3$, 339.0733; found, 339.0732.

*4.1.5.5. (6bS,9R,9aR)-9-((S)-1,2-Dihydroxyethyl)-6,6b,9a-trihydroxy-2,3,9,9a-tetrahydro-1H-furo[3′,4′:4,5]furo[2,3-f]chromen-7(6bH)-one (**13c**).* This material was the minor product from reaction of **4** with **11c** and was obtained in 25% yield as a white, amorphous solid. R_f (70% acetone/CH_2Cl_2) 0.75; $[\alpha]_D^{25}$ +10.8 (*c* 0.01, acetone); IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1155.16, 1239.66, 1455, 1511, 1638, 1775, 2959, 2990–3620 (br); ^{1}H NMR (500 MHz, D_2O, δ): 6.03 (s, 1H, Ar–H), 4.46 (d, J=5.4 Hz, 1H, –OC*H*CHOHCH$_2$OH), 4.24 (dd, J=9.8, 6.7 Hz, 1H, –OCHC*H*OHCH$_2$OH), 4.17 (t, J=5.2 Hz, 2H, –OC*H*$_2$CH$_2$CH$_2$–), 3.87 (dd, J=11.8, 4.4 Hz, 1H, –OCHCHOHC*H*$_2$OH), 3.74 (dd, J=11.8, 6.8 Hz, 1H, –OCHCHOHC*H*$_2$OH), 2.54 (t, J=6.3 Hz, 2H, –OCH$_2$CH$_2$C*H*$_2$–), 1.94 (m, 2H, –OCH$_2$C*H*$_2$CH$_2$–); ^{13}C NMR (126 MHz, D_2O, δ): 174.1, 158.3, 156.2, 153.0, 110.6, 101.2, 99.6, 97.3, 83.2, 78.8, 69.1, 67.1, 61.8, 20.7, 17.7; HRMS-ESI (*m*/*z*): [M−H]$^-$ calcd for $C_{15}H_{16}O_9$, 339.0733; found, 339.0731.

*4.1.6. Preparation of (3R,3aS,8bS)-3-((S)-1,2-diacetoxyethyl)-1-oxo-1,3,3a,8b-tetrahydrofuro[3,4-b]benzofuran-3a,6,8,8b-tetrayl tetraacetate (**3**).* (−)-Ascorbyl phloroglucinol **1a** (100 mg, 0.33 mmol) was placed in a round-bottom flask contained distilled pyridine (215 μL), and acetic anhydride (215 μL) was then added. The reaction mixture was stirred for 14 h at rt. At this time, the contents of the reaction vessel were poured into ice water (50 mL), and the resulting solution was extracted with EtOAc (3×10 mL). The organic layers were collected, combined, dried with $MgSO_4$, and concentrated *in vacuo* to give an oil, which was purified via flash silica chromatography using 10% acetone in CH_2Cl_2 as the solvent providing **3** as a white, amorphous solid in 10% yield. Characterization of this material has been reported previously.[11] ^{1}H NMR (600 MHz, $CDCl_3$, δ): 6.71 (d, J=1.6 Hz, 1H, Ar–H), 6.67 (d, J=1.5 Hz, 1H, Ar–H), 5.78–5.59 (m, 1H, –OC*H*CHOHCH$_2$OH), 4.97 (d, J=4.5 Hz, 1H, OCHC*H*OHCH$_2$OH), 4.41 (dd, J=11.8, 4.5 Hz, 1H, OCHCHOHC*H*$_2$OH), 4.26 (dd, J=11.8, 6.3 Hz, 1H, OCHCHOHC*H*$_2$OH), 2.33 (s, 3H, –OAc), 2.28 (s, 3H, –OAc), 2.16 (s, 6H, –OAc), 2.11 (s, 3H, –OAc), 2.09 (s, 3H, –OAc); ^{13}C NMR (151 MHz, $CDCl_3$, δ): 170.5, 169.9, 168.2, 166.5, 166.1, 154.7, 148.4, 168.4, 158.2, 110.2, 109.6, 112.1, 83.9, 82.1, 68.0, 62.7, 21.3, 21.0, 21.1, 21.0, 20.1, 20.0.

Acknowledgements

The authors would like to acknowledge several colleagues from the University of Tennessee, Knoxville. We thank Drs. David C. Baker and Michael D. Best for helpful discussion, as well as Jessica R. Gooding and Amanda L. May (University of Tennessee, Knoxville) for assistance in preparing this manuscript. We are also grateful to Julia K.C. Abbott and Dr. Zheng Lu for assistance in obtaining crystallographic data. Support for this work was provided by start-up funds from the University of Tennessee, Knoxville.

Supplementary data

This material includes 1D and 2D NMR spectroscopic data for all new compounds as well as X-ray crystallographic data for **1b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.102.

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